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Intramolecular monomer-on-monomer (MoM) mitsunobu cyclization for the synthesis of benzofused thiadiazepine-dioxides†

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Abstract

The utilization of a monomer-on-monomer (MoM) intramolecular Mitsunobu cyclization reaction employing norbornenyl-tagged (Nb-tagged) reagents is reported for the synthesis of benzofused thiadiazepine-dioxides. Facile purification was achieved *via* ring-opening metathesis (ROM) polymerization initiated by one of three metathesis catalyst methods: (i) free metathesis catalyst, (ii) surface-initiated catalyst-armed silica, or (iii) surface-initiated catalyst-armed Co/C magnetic nanoparticles.

The ongoing effort in the search for new pharmacophores and small molecular probes is a key feature of modern drug discovery. The Mitsunobu reaction and its variants[1] represent versatile synthetic methods which are pivotal to accessing small molecules for drug discovery.[2] The Mitsunobu reaction is a mild and effective method for the conversion of alcohols into a variety of functionality through the formation of C–C, C–O, C–N and C–S bonds, including the ability to invert the stereochemistry of stereogenic carbinol-bearing centers. A formal "redox" reaction, the Mitsunobu reaction is promoted under relatively mild conditions by a combination of a tertiary phosphine, usually triphenylphosphine (PPh_3) and an azodicarboxylate, usually diethyl or diisopropyl ester (DEAD or DIAD). Such is the scope of the Mitsunobu reaction, its application has played a pivotal role in the synthesis of natural products,[3] and bioactive small molecules.[4] Despite these powerful attributes, the Mitsunobu reaction suffers from the need for tedious purifications to isolate the desired product, an operational disadvantage in both high-throughput chemistry and natural prodcut synthesis. Addressing this issue, several variants of the Mitsunobu reaction have been developed which include tagged, immobilized and water-soluble reagents that allow for facile separation of the desired product from unwanted Mitsunobu by-products.[5]

Methods developed within our group for facile purification-free Mitsunobu protocols have focused on the application of a polymer-on-polymer (PoP) Mitsunobu protocol, employing

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ROMP-derived oligomeric triphenylphosphine (OTPP) and oligomeric benzylethyl azodicarboxylate (OBEAD) reagents,[6] as well as a monomer-on-monomer (MoM)Mitsunobu protocol, employing norborneneyl-tagged (Nb-tagged) PPh_3 and BEAD reagents.[7] In the latter case, facile sequestration of the excess and spent reagents was achieved *via* ring-opening metathesis (ROM) polymerization initiated by any one of three methods utilizing Grubbs catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh cat-**B**]:[8] (i) free catalyst in solution, (ii) surface-initiated catalyst-armed silica,[9,10] or (iii) surface-initiated catalyst-armed carbon-coated (Co/C) magnetic nanoparticles (Nps) (Scheme 1).[7,11]

The intramolecular Mitsunobu reaction has been widely utilized as a cyclization protocol for the synthesis of heterocyclic molecules.[12] Building on these reports, we herein report the synthesis of benzofused thiadiazepine-dioxides *via* an intramolecular 7-membered MoM Mitsunobu cyclization reaction, whereby facile purification was achieved utilizing ROMP sequestration initiated by free metathesis catalyst or catalyst-armed particle surfaces (Scheme 2).

The synthesis of benzofused thiadiazepine-dioxides **3a** and **3b** was investigated utilizing the intramolecular MoM Mitsunobu cyclization with the readily prepared Nb-tagged PPh_3 (Nb-TPP) and DEAD (Nb-BEAD) reagents.[6] The corresponding hydroxy-benzylsulfonamide starting materials **2a** and **2b** were rapidly generated *via* a microwave-assisted S_NAr protocol (Scheme 3).[13]

With sulfonamides **2a–b** in hand, the application of MoM cyclization reaction was investigated utilizing Nb-TPP and Nb-BEAD (Table 1). Initially, purification was achieved by phase switching of all Nb-tagged species in solution (monomeric reagents and spent reagents) by addition of free metathesis catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh, cat-**B**] (Method **A**) to induce ROM polymerization. The ROM polymerization event was followed by precipitation to produce the desired benzofused thiadiazepine-dioxides **3a** and **3b** in good yield and excellent crude purity (Table 1, entries 1–2). Purification was followed by TLC analysis, whereby the typical Mitsunobu multispot crude reaction mixture was reduced to a single spot after utilizing this polymerization sequestration protocol. Despite this success, the need for precipitation of the crude reaction mixture to remove the polymerized reagents/spent reagents was deemed not ideal for a high-throughput appproach. Therefore, alternative syntheses of benzofused thiadiazepine-dioxides **3a** and **3b** were investigated utilizing a catalyst-armed surface generated from either Nb-tagged Co/C magnetic particles, or Nb-tagged silica particles.

After polymerization sequestration of excess reagents/spent reagents on the surface of the magnetic Co/C beads [Method B], **3a** and **3b** could be obtained in reasonable crude purity by collecting the nanobeads with an external magnet, decanting the solution and evaporating the solvent (Table 1, entries 3–4). Noteworthy, this work-up procedure is carried out within a few seconds, being an operational advantage to conventional filtration techniques. However, to further improve the product purity the solution was filtered over a silica SPE. As an alternative method, the sequestration by Nb-tagged silica particles [Method C] was applied to generate **3a** and **3b** in comparable yields and purities with simple filtration through Celite® SPE to isolate the desired product, avoiding the need for precipitation (Table 1, entries 5–6). Building on these results, substrate scope was evaluated across all three purification sequestration protocols **A–C** for the synthesis of **3c–3n** *via* MoM Mitsunobu cyclization (Scheme 4). Thus, benzofused thiadiazepine-dioxides **3c–3f** were generated with free cat-**B** [Method **A**], compounds **3g–3j** *via* Nb-tagged Co/C magnetic particles [Method **B**] and benzofused thiadiazepine-dioxides **3k–3n** utilizing Nb-tagged Silica particles [Method **C**].

In conclusion, we have demonstrated the application of a MoM intramolecular Mitsunobu cyclization for the synthesis of bi- and tri-cyclic benzofused thiadiazepine-dioxides. Facile purification of crude reaction mixtures was achieved *via* ROM polymerization sequestration of excess reagents/spent reagents. This was accomplished initially utilizing free metathesis catalyst Cat-**B**, followed by precipitation. The method was further optimized utilizing catalyst-armed surfaces generated from either Nb-tagged Si-particles or Nb-tagged Co/C magnetic nano-particles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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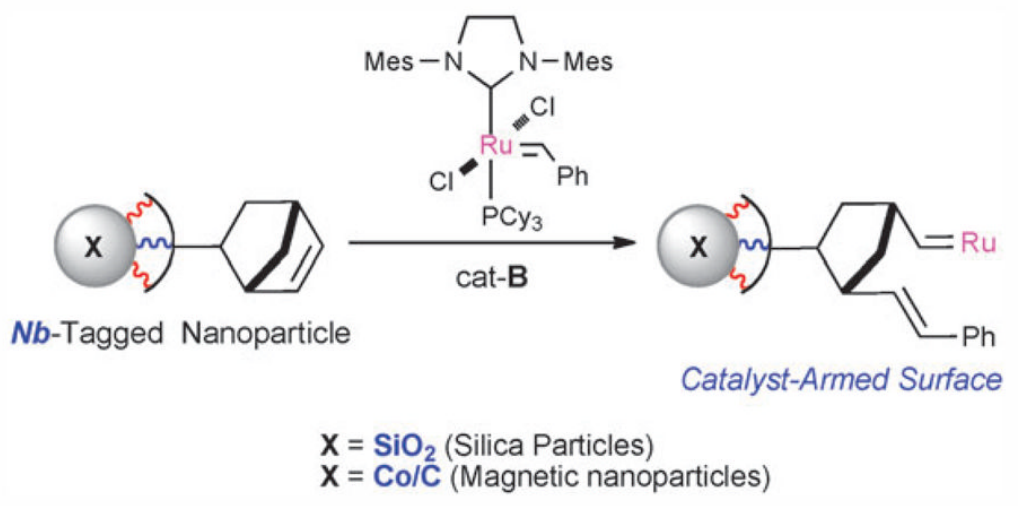
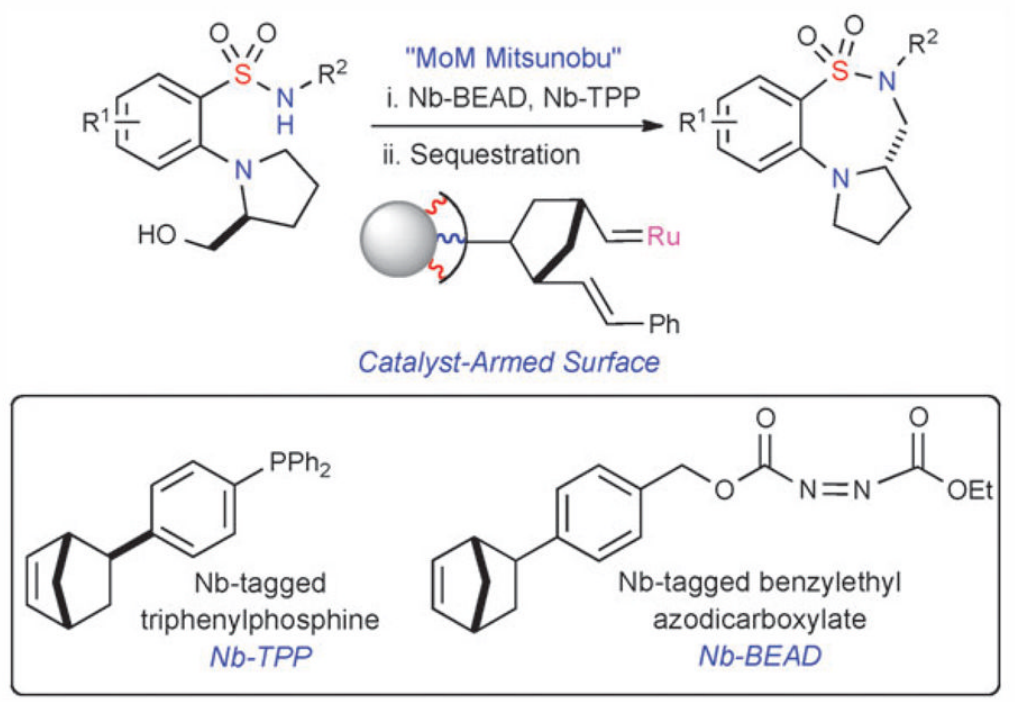
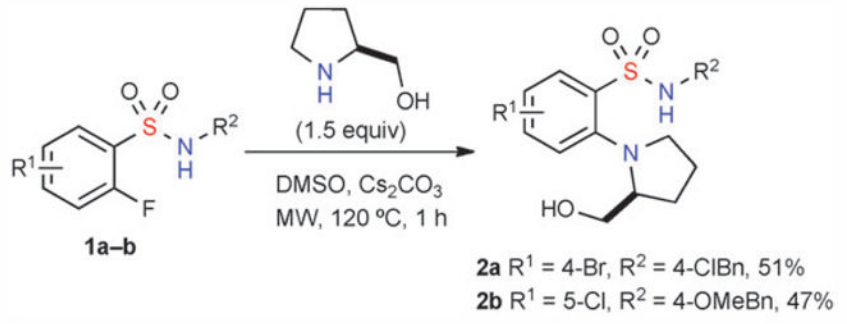


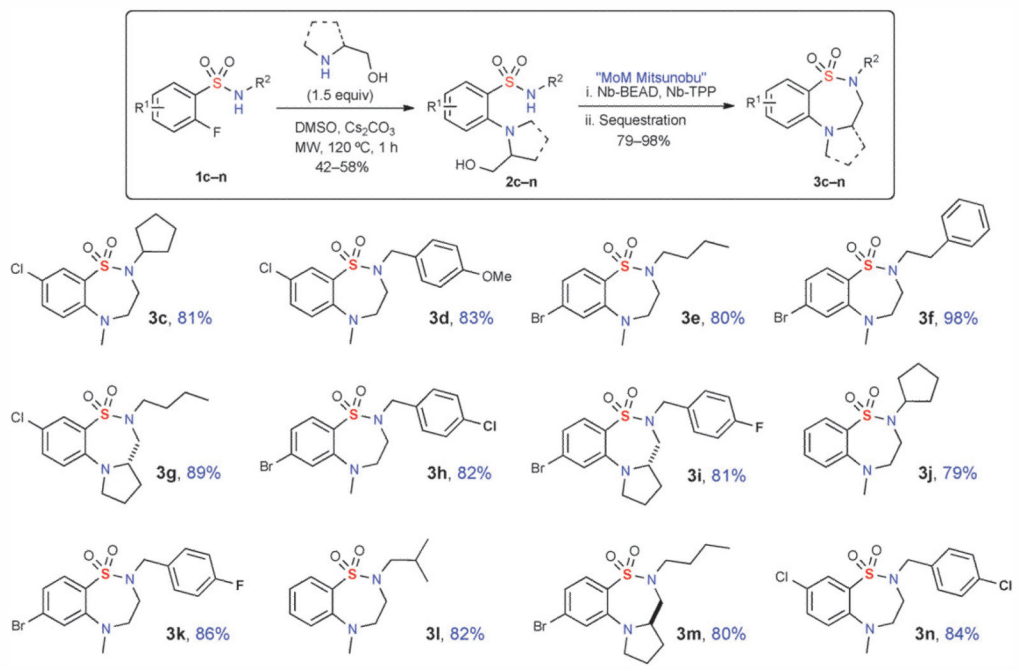
Scheme 1.
Catalyst-armed Silica- and Co/C magnetic nanoparticles.



Scheme 2.
Synthesis of benzofused thiadiazepine-dioxides *via* a intramolecular MoM Mitsunobu c/yclization.



Scheme 3.
Synthesis of hydroxy-benzylsulfonamides **2a–b** *via* microwave- assisted S_NAr.

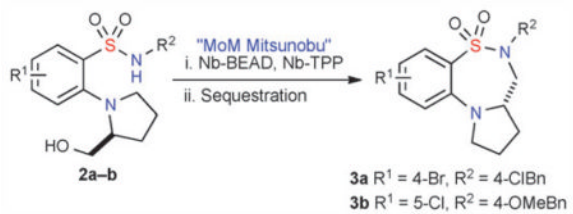


Scheme 4.

Synthesis of benzofused thiadiazepine-dioxides. (**3c–3f**: Method A; **3g–3j**: Method B; **3k–3n**: Method C).

Table 1

Intramolecular MoM Mitsunobu-Sequestration



Entry	Sequestration	Comp.	Method	Yield (%)	Crude Purity (%)[a]
1[b]	Cat-**B**	**3a**	**A**	85	>95%
2[b]	Cat-**B**	**3b**	**A**	88	>95%
3[c]	Co/C Nb-tagged	**3a**	**B**	87	>95%
4[c]	Co/C Nb-tagged	**3b**	**B**	81	>95%
5[d]	Si Nb-Tagged	**3a**	**C**	89	>95%
6[d]	Si Nb-Tagged	**3b**	**C**	84	>95%

[a] Purity determined by ^{1}HNMR.

[b] Isolated *via* precipitation in Et_2O.

[c] Isolated *via* magnetic decantation and filtration through Silica SPE.

[d] Isolated *via* filtration through Celite® SPE.